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**The long arm of childhood intelligence on terminal decline: Evidence from the
Lothian Birth Cohort 1921**

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Disclosure Summary

All the authors declare no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the proposed work.

Abstract

The current study investigates the heterogeneity of cognitive trajectories at the end of life by assigning individuals into groups according to their cognitive trajectories prior to death. It also examines the role of childhood intelligence and education on these trajectories and group membership. Participants were drawn from the Lothian Birth Cohort of 1921 (LBC1921), a longitudinal study of individuals with a mean age of 79 years at study entry, and observed up to a maximum of five times to their early 90s. Growth mixture modelling was employed to identify groups of individuals with similar trajectories of global cognitive function measured with the Mini-Mental State Examination (MMSE) in relation to time to death, accounting for childhood intelligence, education, the time to death from study entry, and health conditions (hypertension, diabetes and cardiovascular disease). Two distinct groups of individuals (classes) were identified: a smaller class (18% of the sample) of individuals whose MMSE scores dropped linearly with about 0.5 MMSE points per year closer to death, and a larger group (82% of the sample) with stable MMSE across the study period. Only childhood intelligence was found to be associated with an increased probability of belonging to the stable class of cognitive functioning prior to death (odds ratio=1.08, standard error=0.02, $p \leq .001$). These findings support a protective role of childhood intelligence, a marker of cognitive reserve, against the loss of cognitive function prior to death. Our results also suggest that terminal decline is not necessarily a normative process.

Keywords: childhood intelligence, education, terminal decline, MMSE, Growth Mixture Models (GMM)

A high priority in today's society is to promote and maintain good physical and mental functions until later in life. Although many older adults preserve their cognitive abilities until the final stages of life, others experience important declines in cognitive abilities before death. Accelerated decline in cognitive function before death is a phenomenon known as terminal decline or terminal drop (TD). TD represents a within-person accelerating loss of mental abilities before death, primarily determined by neurobiological processes and neuropathological changes at the cellular level (Gerstorf & Ram, 2013; Wilson, Segawa, Hitzel, Boyle, & Bennett, 2012). The TD terminology was first proposed by Kleemeier (1962), emphasising a within-person process of faster loss of cognition as individuals approach the end of life.

Published reports demonstrate a variation in findings regarding the onset of the terminal decline process, ranging from 6-7 months to 7-8 years before death depending on the cognitive domain examined (Karr, Graham, Hofer, & Muniz-Terrera, 2018; Muniz-Terrera, Matthews, Stephan, & Brayne, 2011; Piccinin, Muniz, Matthews, & Johansson, 2011; Wilson, Beckett, Bienias, Evans, & Bennett, 2003). This disparity could be driven by the specific biological conditions determining the disease processes leading to death, such as dementia, cardiovascular conditions, cancer, respiratory function, and organ failure (Hassing et al., 2002; Laukka, MacDonald, & Backman, 2006). Furthermore, the differences in findings may be partially explained by the use of different methodologies in the various studies examining terminal decline, the analysis of different cognitive outcomes, and the choice of confounders included in the analyses. In most studies evaluating cognitive changes before death, terminal decline has been regarded as a normative process (i.e. experienced by most individuals facing death in older age), without an in-depth exploration of whether the observed heterogeneity in cognitive trajectories is reflective of hidden subgroups of individuals whose cognitive trajectories follow different patterns of cognitive change prior to death. Moreover, previous reports may have missed the opportunity to identify factors that may be associated with terminal changes, including cognitive functioning measured earlier in life (Wilson et al., 2003).

Higher childhood intelligence and increased levels of education are associated with higher levels of cognitive performance in midlife (Richards & Deary, 2005; Richards & Sacker, 2003; Singh-Manoux et al., 2011), but the evidence with regard to their role in the cognitive decline in the final stages of life is less clear. Childhood intelligence and education represent potential markers of cognitive reserve (Stern, 2002), which represents mental resilience and allows flexible cognitive performance when confronted with the underlying neurodegenerative processes (Stern, 2012).

Intelligence was defined by Gottfredson (1997) as "broader and deeper capability for comprehending our surroundings" (p. 13), which differs from a rather narrow academic skill. Intelligence is conceptualised as a partially heritable trait with a life-long moderately high stability of individual differences (Deary, 2014; Deary, Pattie, & Starr, 2013; Deary, Spinath, & Bates, 2006), whereas education is often regarded as a modifying environmental influence (Deary & Johnson, 2010). Twin and DNA-based studies show that intelligence and educational attainment are heritable to about the same extent and that intelligence and education have a genetic correlation at or above 0.7 (Calvin et al., 2012; Hill et al., 2016).

Childhood intelligence and education have been extensively discussed in the ageing literature (Gale, Allerhand, & Deary, 2012; Hatch, Feinstein, Link, Wadsworth, & Richards, 2007; Richards, Shipley, Fuhrer, & Wadsworth, 2004; Singh-Manoux et al., 2011), although the results are not always consistent. For instance, Richards et al. evaluated the association between childhood cognitive ability and midlife cognition and showed a protective effect of childhood cognitive ability on midlife cognitive decline in adult reading skills (Richards et al., 2004). In contrast, in an investigation of change in cognition using a composite score that included results from Raven's matrices, verbal fluency and logical memory, (Gow et al., 2008) showed a positive association of childhood IQ with the level of cognitive function at age 79, but not with change in cognitive ability to age 83. Using a growth curve analysis, Ritchie and colleagues explored if different domains of cognitive ability age together, or independently according to various factors. They found that higher childhood cognitive ability and more education were associated with a higher level of

cognition at baseline, but not clear protection against steeper declines in any of the cognitive domains investigated (memory, speed, visuospatial and crystallised abilities) (Ritchie et al., 2016).

There is a growing body of research suggesting that childhood intelligence represents a consistent and reliable construct influencing lifelong cognition and subsequent health (Batty, Deary, & Macintyre, 2007; Gow et al., 2012a; Gow et al., 2012b; Johnson, 2012). A possible explanation is that individuals who are higher in intelligence remain intellectually stronger until the end of life, notwithstanding substantial burdens of neocortical and limbic neuropathology associated with ageing (Barnett, Salmond, Jones, & Sahakian, 2006; Colangeli et al., 2016; Esiri & Chance, 2012; Fratiglioni & Wang, 2007; Vance, Roberson, McGuinness, & Fazeli, 2010).

The role of education on cognitive decline in later stages of life is also unclear. This is not the focus of our investigation, but a review of the literature regarding the association of education and cognitive function in older age reported various inconsistencies, with few studies finding a protective effect of education against cognitive decline and several methodological limitations, were highlighted (Lenehan, Summers, Saunders, Summers, & Vickers, 2014). Previous work conducted in the younger Lothian Birth Cohort 1936 investigated whether general or specific aspects of later-life intelligence were associated with longer schooling period. It found some small positive associations between education and specific cognitive capabilities in older age after taking intelligence test score at age 11 into account (Ritchie, Bates, & Deary, 2015). Furthermore, this work built on a previous report, which found that education was positively associated with IQ in older age (70+yrs; after controlling for childhood IQ score), particularly in participants with lower initial IQ scores in later life, and that the association was with IQ but not with arguably more fundamental abilities such as processing speed (Ritchie, Bates, Der, Starr, & Deary, 2013). This overall set of findings indicate that education has the capacity and potential to influence and shape some intellectual capabilities, but perhaps not more fundamental capacities such as the efficiency of more fluid-type cognitive operations such as processing speed.

A pertinent question related to how much intelligence and education influence cognitive changes in later life, particularly terminal decline, remains unclear. To the best of our knowledge, no literature exists regarding the role of childhood intelligence on terminal declines in cognition. Whereas some studies have shown that education offers no real protection in terms of terminal decline in later life (Cadar et al., 2016; Terry & Katzman, 2001), others have found an association with a delayed onset of terminal decline (Batterham, Mackinnon, & Christensen, 2011; Muniz-Terrera, Minett, Brayne, & Matthews, 2014).

In this study, we aim to address two questions. First, we examine whether the decline in global cognitive function before death is a normative process, or experienced by some but not all individuals, and second, we examine the independent and additive roles of childhood IQ and education on global cognitive function before death, in groups of individuals whose end of life trajectories may exhibit different patterns of change.

Method

Participants

The participants were drawn from the Lothian Birth Cohort of 1921 (LBC1921), a longitudinal study of individuals born in 1921. Participants were aged approximately 79 years at study recruitment. Surviving participants who continued to take part in the study were retested at four subsequent test waves at 83, 87, 90 and 92 years of age (approximately 3-yearly intervals). The study design and the specific test-retest intervals were planned and considered in order to capture changes in both cognitive and physical performance in older participants while balancing this against attrition (Deary, Gow, Pattie, & Starr, 2012). Most study participants had previously taken a validated test of intelligence at the age of 11 years in the Scottish Mental Survey of 1932 (Scottish Council for Research in Education [SCRE], 1933). Details of the study can be found in (Deary et al., 2012; Deary, Whiteman, Starr, Whalley, & Fox, 2004; Taylor, Pattie, & Deary, 2018). In brief, the original sample was comprised of 550 individuals (mean age 79 years (SD=0.6)) at wave 1 in 1999/01. They were subsequently tested on four other occasions,

at about mean age 83 in 2003/05 (wave 2), mean age 87 in 2007/08 (wave 3), near to their 90th birthday in 2011/12 (wave 4), and finally at about age 92 in 2013 (wave 5) (Taylor, Pattie, & Deary, 2018). The follow-up study period was up to 14 years. Of the original 550 LBC1921 participants, 321 (58.4%) contributed to the second wave, 235 (42.7%) contributed to the third wave, 129 (23.5%) contributed to the fourth wave, and 59 (10.7%) participated in all waves, including the most recent follow-up at mean age 92 (Wave 5) conducted between April and December 2013. Between, waves 1 and 2, 229 participants were lost from whom 38% died, 26% withdrew, and the remaining lost contact or were not well enough at the time of the interview. A similar pattern was observed for the attrition at subsequent waves. The average rate of attrition from one testing wave to the next was 20% (10% per year) primarily due to death; for more information see (Taylor, Pattie, & Deary, 2018). For the present study, we selected participants who had data on both childhood intelligence and MMSE (Folstein, Folstein, & McHugh, 1975). Participants with a dementia diagnosis at any wave (n=110), identified using data from death certificates or electronic patient records, were excluded from the current analyses. MMSE scores were aligned according to the distance to death. Therefore, only the participants who died during the study period were included in the analytical sample of these analyses (n=444).

Ethical approval was granted for the study by the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and the Lothian Research Ethics Committee (LREC/2003/2/29). Written informed consent was obtained from each participant before testing.

Study variables

The 1921 Lothian Birth Cohort encompassed a broad spectrum of cognitive and behavioural and health measures (Deary et al., 2004). The variables included in their battery assessment were originally selected based on age-relevance and pertinence to different disciplinary perspectives in the epidemiological and gerontological literature.

Childhood intelligence

The cognitive ability of almost every child who had been born in 1921 and was attending school in Scotland was tested on June 1st 1932 (i.e., at about age 11 years) with the Moray House Test (MHT) No. 12 devised by Godfrey Thomson (Deary et al., 2004). The test has high concurrent validity ($r = 0.8$) with an individually administered Stanford-Binet Test. The MHT includes 71 items of various mental tasks were: following instructions (14 items), same-opposites (11), word classification (10), analogies (8), practical items (6), reasoning (5), proverbs (4), arithmetic (4), spatial items (4), mixed sentences (3), cypher decoding (2), and other items (4). When participants were aged 11 years old, the MHT was administered to groups in school, and the test was self-completed under standard instructions given by teachers. Eight practice items preceded the test administration. The test had a time constraint of 45 min, and the maximum possible score is 76. The MHT was concurrently validated in 1947 against the Terman-Merrill revision of the Binet scales and the original MHT scores were corrected for age at testing, then converted to IQ-type scores with a standardised mean score of 100 (SD 15) (Deary & Batty, 2007). Therefore, this test has been well externally validated as a reliable measure of general intelligence (Deary, 2014; Deary et al., 2012; Deary et al., 2004) that shows high rank-order stability across the life-span (Deary, Whalley, Lemmon, Crawford, & Starr, 2000). Within this analytical sample, the childhood intelligence scores ranged between 44 and 130, with the mean of 99 and $SD = 15.21$. We used this score as a continuous measure centred at its mean value in all models.

Education

The number of years of full-time education undertaken by each participant represented their educational attainment, which was recorded for each study member as a continuous measure in all models (centred at its mean value, 10 years).

Mini-Mental State Examination (MMSE)

One of the cognitive tests assessed in later life was the MMSE (Folstein et al., 1975), a measure of global cognitive functioning and one of the most commonly used neuropsychological tests for complaints of memory problems. The test reflected various

mental capabilities such as orientation, memory and attention, the ability to follow verbal and written commands, writing and copying. The MMSE included 21 items, and the maximum score is 30. Participants were mostly tested in a clinical research facility by the LBC1921 team's psychologically trained staff; in the last waves, a few ($n=31$) were tested at home.

Death and time to death

Participant deaths were ascertained at regular intervals, from details supplied by the General Registrar's Office, Scotland. Records of the 500 participants of the Lothian Birth Cohort 1921 study were linked to the National Health Service (NHS) data and flagged when events occurred. Information on vital status and date of death were obtained from the NHS Central Register (NHSCR, Scotland) for participants traced in Scotland and Northern Ireland, and by HSCIC Southport for those located in England and Wales. Time to death was calculated for 444 participants with available data, as the number of years from the study entry until the time of death (range 0 to 14 years).

Covariates

Based on previous findings, we considered sex (women considered as the reference group) and years from study entry to death (centred at its mean value of 8.4 years) as potential confounders.

Participants were asked about their histories of hypertension, diabetes, cardiovascular disease (each coded as 1=yes or 0=no), during a structured medical interview, which took place at the same time as the cognitive testing.

Data analyses

A series of Growth Mixture Models (GMM) were fitted to MMSE scores aligned as a function of time to death to investigate the heterogeneity of MMSE trajectories (Muthén, 2003). GMM is a data-driven analytical method that allows the identification of unobserved groups of individuals (classes) with similar trajectories. The number of classes is unknown a priori, hence, to identify the optimal number of classes in the sample, models with an

increasing number of classes are fitted, and a selection procedure followed. GMM is a flexible method that further permits the adjustment of class-specific trajectory parameters (level and slopes) by covariates and to explicitly model the probability of class assignment using a multinomial or logistic regression, which can also include covariates. Furthermore, these models use Information Maximum Likelihood (FILM) estimation with robust standard errors by making use of all observations in the data and producing the maximum likelihood estimation parameters without imputing data (Graham, 2009).

First, to determine the optimal number of classes, we fitted a series of unconditional models with an increasing number of classes (up to 5) estimating both linear and curvilinear trajectories (e.g., quadratic and cubic slopes). We did not estimate models with more than 5 classes to avoid models with very small classes. Intercepts (the level of MMSE performance) were placed at 2 years before death to ensure interpretability of results and maximise the use of data. Then, standard procedures such as comparison of the lowest BIC indices (Schwarz, 1978), maximum likelihood parameter estimates with robust standard errors (MLR) testing and class interpretation were used to select the optimal model (see Table S1 for BIC values). The class separation was evaluated using the model entropy (Celeux & Soromenho, 1996), an index that takes values between 0 and 1 and that indicates better class discrimination with increasing values.

Finally, after the selection of the optimal model, which was a 2 class linear trajectory, covariates were included on class-specific trajectory parameters (intercept and slopes) and the logistic regression model for a class assignment. Level (intercept) and rate of change (linear slope) were adjusted for demographic characteristics including sex (women used as reference category), age at study entry and time to death from the study entry (centred at 8.4 years to death) as well as the main factors of interest (childhood intelligence and education, which were also centered at the sample mean). Given this model specification, the intercept represents the level of cognitive performance at 2 years before death for a woman, aged 79 with values of zero on all covariates investigated. The class probability model was adjusted for childhood intelligence, education, and other covariates such as sex, distance to death at study entry, and health conditions

(hypertension, diabetes, cardiovascular disease). We controlled for health conditions to understand if there is an independent role of childhood intelligence and education from the effect of poor health on the class membership.

To further disentangle the effects of childhood intelligence from education, a first sensitivity analysis was conducted by excluding childhood intelligence from the models and reassessing the role of education on class membership. A second sensitivity analysis was conducted to investigate the potential ceiling and floor effects on the MMSE by employing a Tobit Growth Model. Finally, a third sensitivity analysis was conducted by examining the terminal decline in the overall sample, including participants with dementia. All models were fitted using MPlus (Muthén & Muthén, 2007) and restricted maximum likelihood (REML) estimation, random slopes and intercepts, and an unstructured covariance matrix. Data from individuals with missing baseline MMSE values ($n=24$) were not included in the analyses.

Results

Studying the characteristics of this population, it was noted that there were slightly more women than men (57%). Table 1 provides a summary of the characteristics of the analytical sample ($n=420$) and participant's characteristics. The average mean years of education was about 10.78 years, which was similar for men and women in this sample.

Table 1 & Figure 1 - about here

A spaghetti plot of the MMSE trajectories as a function of years to death (see Figure 1) depicts the variability in cognitive performance before death. The last cognitive assessment (years to death =0) was considered at a mean of 2 years ($SD=0.59$), before death for each participant. We selected the centering point of 2 years before death with the purpose of ensuring that there were enough individuals who contributed data to the estimation of the intercept. The mean MMSE value at the last assessment in the overall

analytical sample was $M=26.57$ and $SD=3.19$. After model selection procedures (comparison of BIC values, evaluation of class interpretation and MLR testing), a 2-class model describing linear change was identified as the best fitting model (see Table 2 for parameter estimates). For this model, the entropy was 0.763, a value that suggests reasonable, but not optimal class discrimination. A large class comprising over (82%) of the sample was identified as stable in cognitive performance prior to death, in addition to a small and slow declining group in terms of terminal decline (18%). In the stable class, individuals had on average, a high level of function two years before death (β *intercept*=28.26; standard error (SE)=0.17 MMSE points) and experienced a very small annual decline (β *slope*=-0.05 (SE=0.03)) as they approach death. In contrast, individuals in the small class had poorer MMSE scores two years before death (β *intercept*=24.42 (SE=1.04) MMSE points) and exhibited an annual decline of about half MMSE points per year closer to death (β *slope*=-0.44 (SE=0.14)). Figure 2 presents spaghetti plots and the overall model-predicted trajectories of terminal decline in MMSE for the stable and decliners' classes. Figure S1 (supplementary material) depicts the overall model predicted MMSE trajectories for both classes for an individual with values in all covariates.

Table 2 & Figure 2 - about here

Childhood intelligence and education did not emerge as significantly associated with the level of cognitive performance prior to death (childhood intelligence - intercept 'stable class' $\beta=-0.01$, SE=0.01, $p=.70$, childhood intelligence - intercept 'decliners class' $\beta=0.04$, SE=0.04, $p=.27$; education - intercept 'stable class' $\beta=0.04$, SE=0.01, $p=.40$, education - intercept 'decliners class' $\beta=-0.40$, SE=0.49, $p=.42$) or the rate of terminal decline on the linear slopes in either class (see table 2 for the results). In the large stable class, individuals who entered the study closer to death performed slightly better than those who entered the study further from death ($\beta=0.05$, SE=0.03, $p=.04$), a result that suggests a small healthy survivor effect. None of the other factors examined emerged as associated with the level or rate of change in either class.

Regarding the effect of factors on class probability assignment, childhood intelligence was found to be significantly associated with increased odds of being in the large stable class than in the small class of declining individuals, independent of education and other health-related factors (see table 3 for the results). Specifically, an increase of 1 point from the mean value of 99 on the childhood intelligence score, was associated with an 8% increase likelihood of being in the stable class compared to the declining class (odds ratio (OR) =1.08, SE=0.02, $p \leq .001$). Figure 3 presents the probability of the class assignment for each of the stable and decliners classes.

Table 3 & Figure 3 - about here

The results of the first sensitivity analysis performed (results presented in supplementary material Table S2) showed that education had a significant association with stable class membership when childhood intelligence was not included in the models. This implies that, with each additional year of education from the average value of 10 years, the odds of being in the stable class were increased with 54% compared to the class of decliners (odds ratio (OR)=1.54 SE=0.11, $p \leq .001$). The results of the second sensitivity analysis in which we employed a Tobit Growth Model (see Table S3 & S4) in order to investigate the potential ceiling and floor effects on the MMSE showed a similar pattern of results as with our main analyses in which we employed Growth Curve Models. Lastly, the results of our third sensitivity analysis conducted in the overall sample, including participants with dementia during the study also corroborate with the main results, perhaps due to a lower number of individuals with dementia in this study (see Table S5 & S6).

Discussion

The current analyses had examined the heterogeneity of MMSE trajectories before death in a narrow-age cohort whose childhood intelligence scores were available and who were studied from an average age of 79 years old into their 90s. We identified distinct patterns of change as individuals approached death and described the associations of childhood intelligence and education with these patterns after accounting for individual differences in age at baseline, sex and distance to death at study entry. Our results identified a large stable high functioning class and a small class of slow decliners who had poorer MMSE performance before death compared with individuals in the stable class. Of the factors examined in relation to the class assignment, which included highly prevalent health conditions such as cardiovascular disease, diabetes, and hypertension, only childhood cognitive ability emerged as associated with an increased probability of being in the stable class.

The terminal decline hypothesis postulates an acceleration in the rate of cognitive decline before death. Our results indicate that, in this sample of participants from the LBC1921, who remained free of dementia until death, the terminal cognitive decline was not evident for everyone. This may be the result of the relatively healthy nature of the cohort studied, which has been previously reported (Deary et al., 2012; Gow et al., 2012). These results could be interpreted as providing support to the hypothesis postulated by MacDonald, Hultsch and Dixon (2011), who proposed that terminal declines may be reflective of pathological processes such as dementia, cardiovascular disease, and cancer, and less evident in healthy population samples. However, in a set of other sensitivity analysis of the full sample including individuals who developed dementia during the study follow up, results remained fairly similar, perhaps due to the low number of dementia cases in this cohort. Another evaluation of the LBC1921 provided evidence that unrecognised dementia had little or no effect on various determinants of lifetime cognitive ageing, including childhood intelligence (Sibbett, Russ, Pattie, Starr, & Deary, 2018).

To the best of our knowledge, this is the first investigation of the role of childhood intelligence on trajectories of cognitive performance at the end of life. Our results indicate that individuals with higher childhood intelligence have a greater probability of being in a

stable class than in the slow declining group after accounting for health conditions and other demographic factors, suggesting a protective role at the end of life. With this, we have documented that childhood intelligence (a substantially heritable trait), has a long-term association with the stability of cognitive performance prior to death, whereas educational attainment was less strongly predictive in these analyses. This seems to be in line with previous ageing reports demonstrating a protective role of childhood intelligence on cognitive performance in later life (Corley, Gow, Starr, & Deary, 2012; Deary, MacLennan, & Starr, 1998; Deary et al., 2004).

An important body of research documents terminal decline trajectories of global cognitive function (Batterham et al., 2011; Cadar et al., 2016; Gerstorf & Ram, 2013; Laukka et al., 2006; Muniz-Terrera et al., 2011; Palmore & Cleveland, 1976; Wilson et al., 2003) and focus on the investigation of education, a commonly used marker of cognitive reserve, on these trajectories. However, only a few of the published results are consistent. For instance, in an evaluation of cognitive reserve on MMSE trajectories of two studies of the oldest old, the Swedish OCTO-Twin study and the British Newcastle 85+ study, Cadar et al. reported that education was only associated with an overall cognitive performance before death in the Swedish, but not the British sample (Cadar et al., 2016). Batterham et al. examined data from participants in the Canberra Longitudinal Study and reported delayed onset of faster decline in global function for individuals with lower education and these individuals declined faster after they entered the rapid declining phase (Batterham et al., 2011). Their results are partially at odds with the typical interpretation of the cognitive reserve hypothesis that suggests a protective effect of education against decline. However, in a previous report that also employed change point modelling, Muniz et al. indicated that more educated individuals who participated in the Cambridge City over 75 Cohort Study experienced a later onset of faster decline of MMSE scores, that they declined at a slower rate before this onset, but that education did not modify the rate of decline in the final phase, results that are more consistent with the reserve hypothesis (Muniz-Terrera et al., 2014). Differences in key features of the populations and design of the longitudinal studies analysed may partially explain these contradictory findings. For

instance, the studies differ in the number and spacing of the assessments (4 occasions approximately 4 years apart over 12 years in the Canberra Longitudinal Study, Australia (Batterham et al., 2011) versus 21 years follow-up with varying periods between the waves of data collection in the Cambridge City over 75 Cohort Study, UK (Muniz-Terrera et al., 2014)). Furthermore, the Canberra sample was younger on average at study entry than the British one and education and other covariates considered in these analyses were measured differently across the studies, which did result in a significant difference with regard to the interpretation of these models' results. To gain a thorough understanding of the differences in these reports, further research is needed, including investigations that employ a coordinated analysis to avoid inconsistencies due to different methodological approaches.

Neither education nor childhood intelligence was found to explain the individual differences between individuals captured within either class in terms of their cognitive function prior to death, or corresponding rates of change. These findings, which are interpreted in the context of the discriminatory effect of childhood intelligence on the class assignment, point towards a life-course effect of childhood cognition (Deary, 2013, 2014), rather than a specific effect as a trajectory modifier at the end of life. Prior evidence from this cohort demonstrated that the shared variance between the word-reading tests (Wechsler Test of Adult Reading, National Adult Reading Test) and MMSE scores, was significantly attenuated after controlling for childhood intelligence, while the subsequent adjustment for education explained little additional variance (Dykier, Der, Starr, & Deary, 2016). However, given that in this study, we investigated the roles of childhood intelligence and education on the MMSE performance prior to death and in relation to terminal decline across the study period within two specific classes (stable vs decliners), it is possible that this methodological approach has resulted in a limited variation in MMSE. Furthermore, although intelligence and education are highly correlated, childhood intelligence at age 11 predicted change in intelligence score several years later (Deary, Strand, Smith, & Fernandes, 2007; Strenze, 2007). However, there is also some evidence for a small effect in the opposite direction, with more education being associated with

higher intelligence test scores (Ritchie & Tucker-Drob, 2018). In addition to phenotypic associations, both intelligence and education are partly heritable and have a high genetic correlation (Davies et al., 2018; Davies et al., 2019). We have previously reported, in the LBC1921 sample, on the interplay between childhood intelligence and education (as well as paternal education and social class) in their associations with life outcomes such as adult occupational social class (Johnson, Brett, & Deary, 2010), and later-life IQ (Ritchie et al., 2013). In the younger LBC1936, we found that education had a small association with intelligence at age 70 even after taking into account intelligence at age 11 and adult social class (Johnson, Gow, Corley, Starr, & Deary, 2010), and with specific cognitive capabilities (Ritchie et al., 2015). Therefore, it is not easy to separate putative effects of prior intelligence and education, which are reciprocally and dynamically associated from childhood to older age and have both environmental and genetic contributions to their associations. We also note that some of the strengths of associations between intelligence and education with other variables are difficult to straightforwardly compare because intelligence is measured on a continuous scale and education tends to have cruder assessments. We have previously discussed these matters at length (Deary & Johnson, 2010), and offered various causal accounts and potential mechanisms. The “system integrity” hypothesis is one account, which proposes that childhood intelligence is one indicator of a healthy body more generally and is thereby related to later health outcomes, cognition and mortality (Deary, 2012). Some indirect support for this comes in the evidence of there being some genetic correlations between education, intelligence, health and survival (Deary, Harris, & Hill, 2019; Yang et al., 2010).

With respect to the other variables examined in relation to class-specific trajectories, only distance to death at study entry was found to be significantly associated with the performance before death in the class of individuals with stable MMSE scores. That is, individuals who entered the study closer to death performed better than those who entered the study further from death, a result that is indicative of a healthy survivor effect as previously documented in other studies of terminal decline (Piccinin et al., 2011), yet it is possible that estimates of the association of covariates on the declining class-

specific trajectory parameters did not reach conventional significance thresholds because of the small number of individuals in that class.

Strengths and limitations

The most important aspects of these analyses are the investigation of heterogeneity of global cognition trajectories at the end of life, and the opportunity to detect evidence of variance in proximity to death due to early indicators of childhood intelligence and education. A strength of the analysis is the ability to consider childhood cognitive ability, information that is not available in most longitudinal studies of older adults. Another strength is the narrow spread of ages at baseline in the cohort, which largely avoids the confounding effect of age. Furthermore, in Lothian Cohort, the interval of testing is approximately 3-yearly intervals. Although this seems relatively a long retest interval, there are important advantages considered in the longitudinal framework of cognitive ageing. First of all, the study provides important follow-up measures, without a higher risk of practice effects, usually encountered when the follow-up period is relatively close within a one-year interval or less.

As potential limitations, we acknowledge that, although we evaluated both childhood intelligence and education to assess the role of cognitive reserve, we did not control for a number of other potential confounding factors in our models and, as a consequence, we might have missed a number of unobserved factors (e.g., cognitively engaging jobs and hobbies) that could also have contributed to an individual's cognitive reserve across the life course. We also acknowledge that it is possible that our results could have been affected by limitations that arise from the relatively long retest interval of the Lothian Cohort study 1921. Furthermore, the reliance on the MMSE may have limited our ability to capture terminal decline. For instance, it is possible that individuals captured in the large stable class were more likely to be at ceiling performance. Nonetheless, even when investigating them with Tobit models, our results remained consistent, demonstrating a certain level of heterogeneity in the cognitive trajectories

before death. We also acknowledge that, within the confines of this dataset, there may have been a limited potential to distinguish between true stability before death versus relatively late and rapid decline in the apparently "stable class". Another study limitation constitutes the methodology of diagnosing dementia in this cohort, based on the death certificates and medical records, which may have lacked sensitivity, although work by Sibbett et al., (2018) has shown that most studies examining nonpathological influences on cognitive ageing on LBC 1921 appeared not to have missed too many dementia cases that would have been expected in this sample, given epidemiological estimates (Sibbett, Russ, Deary, & Starr, 2017a; Sibbett, Russ, Deary, & Starr, 2017b). Lastly, attrition and healthy survivor effects are standard limitations that affect longitudinal studies of older adults. The LBC1921 cannot avoid these issues. However, it has the strength that is a subset sample of a nation-wide Scottish assessment of the intelligence of those born in 1921 that tested almost the whole population. This means that we know how the LBC1921's intelligence test scores at age 11 compare with the entire background population. The mean (SD) of the Moray House test in LBC1921 is 46.4 (11.9; (Deary, Whiteman, Starr, Whalley, & Fox, 2004)) versus 34.5 (15.5; (Maxwell, 1961, p.22), for the whole of Scotland. Thus, the LBC 1921, at its outset, had a higher mean and smaller standard deviation than the background population. In addition to the characteristics of those who take part in longitudinal studies, this probably also indicates a survivor effect, considering the participants' age (79 years) at the study recruitment and the fact that the Moray House Test score at age 11 in the whole 1921-born Scottish population is associated with survival to older age (Whalley & Deary, 2001). In the LBC1921 sample, specifically, change in Moray House Test Score between age 11 and age 79 was associated with survival from age 79 to 89 (Murray, Pattie, Starr, & Deary, 2012). Despite the current limitations presented, the sample examined is arguably valuable, as there are very few studies in the world that have information about childhood IQ and cognitive functioning in later life that permits longitudinal investigations of childhood IQ and education on the terminal decline. Therefore, the rarity of this information adds value to the work reported.

An important direction for future research will be to examine the interactions between genetic and environmental determinants of terminal decline, given that childhood intelligence could also determine selection in higher education and other macro-environmental contexts, such as socioeconomic status (Hill et al., 2016). Further work should also explore the heterogeneity in terminal decline with other cognitive measures available.

Conclusion

We found that higher childhood intelligence has a long-term association with the level of cognitive function, even at the end of life. The current results demonstrate a certain degree of heterogeneity as marked by the two-class results of terminal decline trajectories in this Scottish sample, which was drawn from a nationwide, whole-year-of-birth cognitively tested population in childhood, and also benefits from a wealth of neuropsychological data in their later life. We had highlighted the importance of childhood intelligence on the group membership, which was characterised by the stability of cognitive functioning prior to death, whereas educational attainment and other environmental influences were less influential when childhood intelligence was taken into account. Finally, to the extent that intelligence may be malleable to some degree across life (Ritchie & Tucker-Drob, 2018), the current findings could have implications for public health policy and interventions. One possible implication is that early interventions for mental development should start as early as childhood, in order to be the most effective across the entire span of life with long-term benefits for the preservation of cognitive abilities until the end of life.

Data availability

For more information on the Lothian Birth Cohorts (LBC) 1921 and 1936 data access, please visit their website <https://www.lothianbirthcohort.ed.ac.uk/>.

The LBC study data have been the subject of many internal and external collaborations, which are encouraged. The current procedure for those who wish to work with the data is initially to email Professor Ian Deary (I.Deary@ed.ac.uk) to ask for an 'LBC Data Request Form'.

Author Note

Preliminary findings of this work have been presented as part of an international conference symposium: The Geriatric Society for America in Austin, Texas, 13-17th November 2019.

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Table 1. Characteristics of the analytical sample

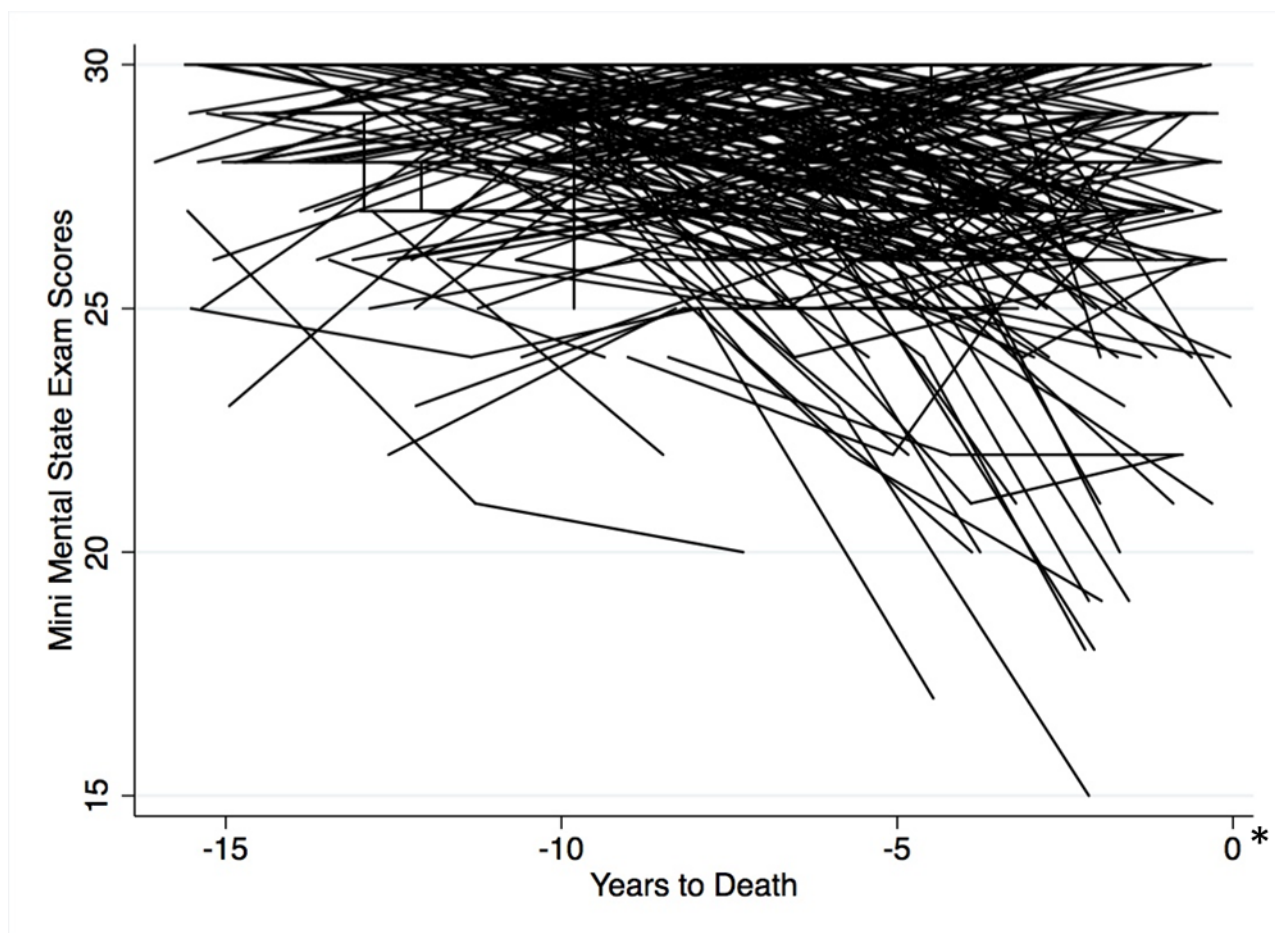
	Total sample		Men		Women	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
MMSE 1	420	28.04 (1.75)	187	27.93 (1.85)	233	28.13(1.65)
MMSE 2	222	27.82 (2.08)	105	27.78 (1.90)	117	27.87(2.23)
MMSE 3	121	27.29 (2.51)	63	27.17 (2.59)	58	27.41(2.45)
MMSE 4	58	26.50 (3.13)	29	25.38 (3.70)	29	27.62(1.91)
MMSE 5	15	26.07 (2.52)	7	27.42 (1.27)	8	24.88(2.80)
Childhood intelligence	420	99.36 (15.20)		99.04 (15.65)		99.60 (14.87)
Years of education	420	10.78 (2.38)	187	11.03 (2.67)	233	10.61 (2.15)
Years to death from baseline	420	-8.41 (4.08)	187	-8.07 (4.22)	233	-8.67 (3.97)
Hypertension	420	42.15%	187	40.21%	233	43.73%
Diabetes	420	6.01%	187	6.81%	233	5.41%
CVD	420	30.51%	187	40.02%	233	23.31%

Table 2. Results of the growth mixture model fitted to Mini-Mental State Scores

				Stable class			Decliners class		
				N=345 (82%)			N=75 (18%)		
				<i>β Coef.</i>	<i>SE</i>	<i>p-value</i>	<i>β Coef.</i>	<i>SE</i>	<i>p-value</i>
Intercept	(MMSE level before death)			28.26	0.17	.001	24.42	1.04	.001
	Childhood intelligence (centred)			-0.01	0.01	.70	0.04	0.04	.27
	Education- years (centred)			0.04	0.05	.40	-0.40	0.49	.42
	Men versus women			-0.32	0.21	.13	-1.11	0.81	.17
	Age at study entry (centred)			-0.12	0.18	.06	-0.78	0.69	.26
	Years to death from baseline			0.05	0.03	.04	0.16	0.09	.08
Linear slope				-0.05	0.03	.08	-0.44	0.13	.001
	Childhood intelligence (centred)			-0.01	0.01	.50	-0.01	0.01	.78
	Education- years (centred)			-0.01	0.01	.27	-0.05	0.04	.17
	Men versus women			-0.01	0.03	.87	-0.18	0.14	.18
	Age at study entry			0.01	0.03	.98	-0.16	0.12	.27
	Years to death from baseline			0.01	0.01	.29	-0.02	0.02	.31
Residual variances									
	Intercept			1.09	0.31	.001	1.09	0.31	.01
	Linear slope			0.01	0.01	.10	0.01	0.01	.10

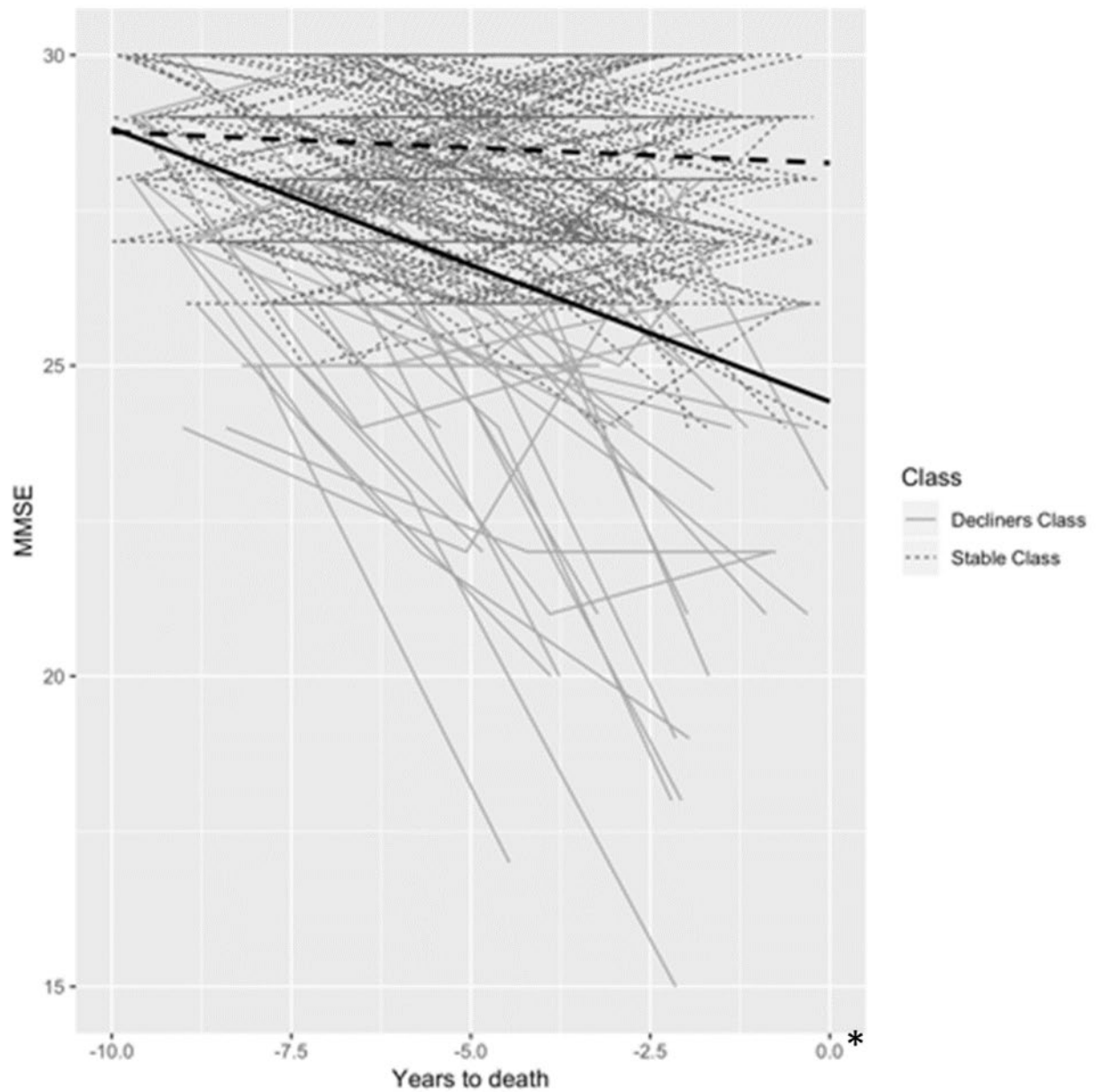
Table 3. The odds ratios (OR) of being in the stable vs decliners' class

	OR	SE	p-value
Childhood intelligence (centred)	1.08	0.02	.001
Education years (centred)	1.16	0.15	.51
Men versus women	1.32	0.49	.57
Age at study entry (centred)	2.08	0.40	.23
Years to death from baseline	1.04	0.06	.33
Hypertension	1.11	0.44	.89
Diabetes	0.78	0.79	.65
Cardiovascular disease	1.33	0.46	.57



**The last cognitive assessment (years to death =0) was considered at 2 years before death*

Figure 1 Spaghetti plots of observed MMSE scores plotted as a function of distance to death



*The last cognitive assessment (years to death =0) was considered at 2 years before death

Figure 2. Spaghetti plots and model-predicted trajectories of terminal decline in MMSE for the stable and decliners classes

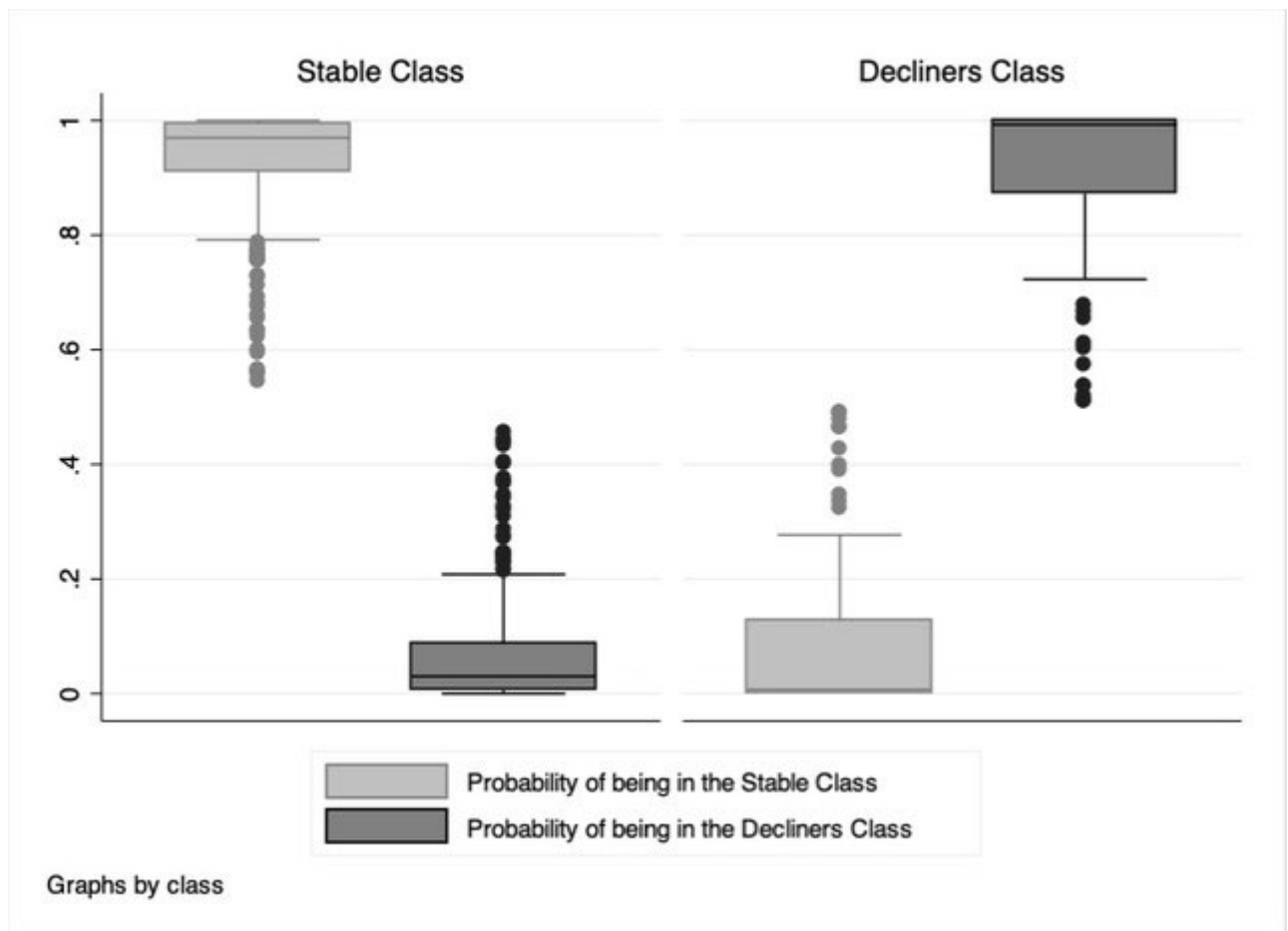


Figure 3. Box plots of the probability of class assignment of individuals assigned to the stable (left panel) and decliners (right panel) classes

Supplementary material

Table S1. Log odds of being in the stable vs decliners' class, models without childhood intelligence

Number of Classes	BIC	Entropy
1	117197.3	NA
2	11471.42	0.76
3	11525.67	0.62
4	11590.36	0.64
5	11695.64	0.63

Table S2. Log odds of being in the stable vs decliners' class, models without childhood intelligence (sensitivity analysis I)

	OR	SE	p-value
Education- years (centred)	1.54	0.11	.001
Men versus women	0.77	0.42	.59
Age at study entry (centred)	2.03	0.40	.23
Years to death from baseline	1.08	0.06	.15
Hypertension	1.11	0.38	.17
Cardiovascular disease	1.31	0.43	.54
Diabetes	0.80	0.79	.77

Table S3. Results of the Tobit growth mixture model fitted to Mini-Mental State Scores (sensitivity analysis II)

				Stable class			Decliners class		
				N=375 (82%)			N=45 (18%)		
				β Coef.	SE	p-value	β Coef.	SE	p-value
Intercept	(MMSE level before death)			28.16	0.21	.001	23.23	2.01	.001
	Childhood intelligence (centred)			-0.01	0.01	.91	0.04	0.07	.53
	Education- years (centred)			0.07	0.07	.28	-0.32	0.73	.66
	Men versus women			-0.27	0.28	.34	-1.13	1.25	.37
	Age at study entry (centred)			-0.11	0.26	.66	0.39	1.40	.78
	Years to death from baseline			0.07	0.04	.03	0.35	0.16	.03
Linear slope				-0.08	0.03	.02	-0.64	0.23	.005
	Childhood intelligence (centred)			-0.01	0.01	.08	-0.01	0.01	.87
	Education- years (centred)			-0.01	0.01	.15	-0.04	0.09	.65
	Men versus women			0.01	0.04	.97	-0.28	0.16	.08
	Age at study entry			0.01	0.04	.90	0.20	0.19	.29
	Years to death from baseline			0.01	0.01	.31	-0.02	0.02	.27
Residual variances									
	Intercept			2.11	0.44	.001	2.11	0.44	.001
	Linear slope			0.01	0.01	.004	0.01	0.01	.004

Table S4. Log odds of being in the stable vs decliners' class, Tobit models (sensitivity analysis II)

	OR	SE	p-value
Childhood intelligence	1.08	0.02	.001
(centred)			
Education- years (centred)	1.06	0.16	.72
Men versus women	1.08	0.61	.90
Age at study entry (centred)	2.03	0.40	.05
Years to death from baseline	1.03	0.09	.78
Hypertension	0.91	0.66	.89
Cardiovascular disease	1.23	0.51	.71
Diabetes	0.58	1.66	.67

Table S5. Results of the growth mixture model fitted to Mini-Mental State Scores including participants with dementia (sensitivity analysis III)

				Stable class			Decliners class		
				N=348 (81%)			N=86 (19%)		
				β Coef.	SE	p-value	β Coef.	SE	p-value
Intercept	(MMSE level before death)			28.26	0.18	.001	24.60	1.06	.001
	Childhood intelligence (centred)			-0.01	0.01	.87	0.04	0.04	.27
	Education- years (centred)			0.03	0.05	.59	-0.42	0.49	.40
	Men versus women			-0.32	0.22	.15	-1.15	0.79	.15
	Age at study entry (centred)			-0.10	0.19	.59	-0.39	0.81	.63
	Years to death from baseline			0.05	0.01	.87	0.15	0.12	.19
	Dementia during study period			-5.71	2.59	.03	-9.38	0.01	.99
Linear slope				-0.06	0.03	.05	-0.37	0.14	.006
	Childhood intelligence (centred)			0.04	0.04	.27	-0.01	0.01	.85
	Education- years (centred)			-0.42	0.49	.40	-0.05	0.04	.17
	Men versus women			-1.15	0.79	.15	-0.18	0.15	.22
	Age at study entry			-0.39	0.81	.63	-0.11	0.15	.49
	Years to death from baseline			0.15	0.12	.19	-0.01	0.03	.59
	Dementia during study period			0.06	0.68	.93	-3.62	0.01	.99
Residual variances									
	Intercept			1.19	0.34	.001	1.19	0.34	.001
	Linear slope			0.01	0.01	.03	0.01	0.01	.03

Table S6. Log odds of being in the stable vs decliners' class: Results of the growth mixture model fitted to Mini-Mental State Scores including participants with dementia (sensitivity analysis III)

	OR	SE	p-value
Childhood intelligence (centred)	1.08	0.03	.003
Education- years (centred)	1.19	0.17	.28
Men versus women	1.35	0.67	.61
Age at study entry (centred)	2.03	0.40	.05
Years to death from baseline	1.05	0.07	.45
Hypertension	1.08	0.47	.86
Cardiovascular disease	1.39	0.65	.55
Diabetes	0.62	0.50	.45

The long arm of childhood intelligence on terminal decline



**The last cognitive assessment (years to death =0) was considered at 2 years before death*

Figure S1. Model-predicted trajectories of terminal decline in MMSE for the Stable and Decliners Classes for an individual with values in all covariates (main analyses)